## ***REMARKS***

Claim 21 has been cancelled without prejudice to its subsequent introduction into this application or its introduction into a related application. Upon entry of this paper, claims 1-18 will be pending and under consideration in this application.

According to the outstanding Office Action, it appears that the rejection of claims 1-18 and 21 under 35 U.S.C. §112, second paragraph has been removed. Furthermore, it appears that the rejection of claims 1-7, 11 and 18 under 35 U.S.C. §102(b) in view of Matsuo *et al.* (1996) has been withdrawn. Also, it appears that the rejection of claim 15 under 35 U.S.C. §103(a) in view of Matsuo *et al.* (1996) and Faktorovich *et al.* (1990) has been withdrawn.

Applicants wish to thank Examiner Falk for the courtesy extended and for the insightful comments about the case during a telephonic interview with the undersigned that took place on June 29, 2004. During the interview, the outstanding written description and enablement rejections were discussed. Applicants agreed to submit experimental data in declaratory form for consideration by the Examiner. The substance of the interview is incorporated in this paper.

The remaining rejections are addressed in the order in which they appear in the outstanding Office Action.

### ***Rejection of Claim 21 Under 35 U.S.C. §112, First Paragraph***

According to page 3 of the Office Action, claim 21 presently stands rejected for lack of written description. The Office Action alleges that claim 21 constitutes new matter. Applicants respectfully traverse this rejection for the following reasons.

Applicants believe that ample support for claim 21 can be found, for example, at page 6, line 25; page 7, lines 8-10; page 8, lines 2-4; page 32, lines 19-21; and page 34, lines 11-12 of the application as filed. The Office alleges that the specification fails to "specifically refer to a nucleic acid that reduces development of choroidal neovascularization." Applicants submit, however, that it is well settled that "*ipsis verbis* disclosure is not necessary to satisfy the written description requirement of section 112. Instead, the disclosure need only reasonable convey to persons skilled in the art that the inventor had possession of the subject matter in question."

*Fujikawu v. Wattanasin* 93 F. 3d 1559, 39 USPQ 2d 1895 (Fed. Cir. 1996). Moreover, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 76 F. 3d 1168, 37 USPQ 2d 1578 (Fed. Cir. 1996).

Applicants submit that the portions of the specification identified herein reasonably convey to persons skilled in the art that the inventors were in possession of the subject matter of claim 21. For example, page 32, lines 19-21 of the application states that anti-angiogenic drugs, for example, nucleic acids (see, for example, page 6, line 25 and page 7, line 10) may be used to prevent choroidal neurovascularization (CNV). However, without acquiescing to the merits of this rejection but in order to promote prosecution, Applicants have cancelled claim 21 without prejudice to its subsequent introduction into either this or a related application, and without any intention of abandoning the claimed subject matter.

In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

***Rejection of Claims 1-18 and 21 Under 35 U.S.C. §112, First Paragraph***

According to pages 4-6 of the outstanding Office Action, claims 1-18 and 21 presently stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Office Action alleges that the specification fails to enable one skilled in the art to practice the claimed invention. Applicants respectfully traverse this rejection for the following reasons.

The test for enablement is whether persons skilled in the art can make and use the invention without undue experimentation (see, for example, MPEP 2164.01 and MPEP 2164.02). Applicants submit that the claims are not unduly broad and that the skilled artisan, after reading the instant application, would be fully enabled to carry out the claimed invention.

Applicants submit that the claimed invention is directed to a method of delivering a nucleic acid molecule into the interior of a mammalian eye. The method, according to claim 1 for example, comprises contacting a scleral (outer) surface of the eye with a nucleic acid

molecule having a molecular weight no greater than 150 kDa such that the nucleic acid passes through the sclera and into the interior of the eye.

Applicants submit that the specification complies fully with the requirements of 35 U.S.C. §112, first paragraph as it provides a detailed description of how to apply a therapeutic or diagnostic agent, for example, a nucleic acid molecule, to the outer surface of the eye for transfer through the sclera, and to methods for actually detecting transfer of molecules of interest through the sclera (see, for example, the paragraph bridging pages 11 and 12, and Examples 1-5 and 8). Specifically, Applicants submit that the skilled artisan using, for example, the *in vitro* diffusion apparatus and the associated protocol described in Example 1 could readily determine -- without any undue experimentation whatsoever -- whether a nucleic acid having a molecular weight no greater than 150 kDa can pass through scleral tissue.

In the September 19, 2003 submission, Applicants indicated that the specification clearly discloses how to apply nucleic acid to a scleral surface and that this was all that was required for the nucleic acid to traverse the sclera. The Office disagreed and stated that the "specification must teach how to use the claimed invention," and that the "nucleic acid must pass through the sclera and into the interior of the eye." Applicants respectfully submit that the specification provides a detailed description of how to use the claimed invention in accordance with 35 U.S.C. §112, first paragraph. As discussed above, Applicants submit that the specification describes how to apply a nucleic acid to a scleral surface, and how to test without any undue experimentation (for example, by following the protocol described in Example 1 of the application as filed) whether a nucleic acid having a molecular weight no greater than 150 kDa can pass through the sclera.

Notwithstanding, Applicants enclose an executed declaration by Karen G. Carrasquillo, Ph.D. The declaration describes an *in vivo* experiment that demonstrates that a nucleic acid, an anti-Vascular Endothelial Growth Factor (VEGF) aptamer, can traverse the sclera and then exert a biological effect within the interior of the eye.

Furthermore, the Office Action indicates that the claimed method is not enabling "due to the unpredictability in the 'gene delivery' art." The Office Action goes on to state that the specification of the instant application "does not provide a working example."

To the extent that the Office Action meant to refer to the "gene therapy" rather than the "gene delivery" art Applicants submit that claim 1 is a directed to a method for delivering a nucleic acid into a mammalian eye. As has been discussed previously, Applicants submit that the claims are not necessarily "directed to methods of gene therapy." All that is required is that a particular nucleic acid traverse the sclera and enter the interior of the eye. Applicants submit that the specification provides a detailed discussion of the types and characteristics of molecules that can be delivered transclerally (see, for example, the first full paragraph on page 13 and Example 1). In addition, the specification provides a detailed description of how to apply such molecules to the outer surface of the eye for transfer through the sclera, and methods for actually detecting transfer of molecules of interest through the sclera (see, for example, the paragraph bridging pages 11 and 12, and Examples 1-5 and 8).

To the extent that the Office Action meant to refer to the "gene delivery" art, Applicants submit that the specification, as discussed above, provides a detailed description of how to apply therapeutic and diagnostic agents to the outer surface of the eye for transfer through the sclera, as well as methods for actually detecting the transport of molecules through the sclera. Dr. Carrasquillo's declaration describes an *in vivo* experiment that shows that the anti-VEGF aptamer known as EYE-001, when contacted with the outer scleral surface of a mammalian eye, can traverse the sclera and impart a biological effect, e.g., reduce leakage of blood vessels, within the eye.

Furthermore, the Office Action states that in the poster and Carrasquillo (2003) paper already of record as documents C3 and C18, respectively, the experiments were "not carried out in accordance with the teachings of the specification." The Office Action goes on to state that the poster and article both described the use of "poly (lactic-co-glycolic)acid microspheres for the delivery of an oligonucleotide by transscleral delivery, but the instant specification does not." Furthermore, the Office Action states that the "evidence does not demonstrate delivery without a 'means for facilitating transport of the nucleic acid across the sclera.'" Applicants disagree.

As a threshold matter, Applicants submit that the microspheres used in the paper and poster were being used to provide the nucleic acid being tested to the scleral surface over a period of time. Once released from the microsphere, the nucleic acid could then contact the

scleral surface and then pass through the sclera. Applicants submit that the microspheres provided a reservoir of nucleic acid, which was released into contact with the scleral surface. Applicants submit the microspheres are not required for a nucleic acid to pass through the sclera. To the extent that the *in vivo* experiment described in Dr. Carrasquillo's declaration employed the anti-VEGF aptamer encapsulated in PLGA microspheres, Dr. Carrasquillo in section 6.3 of her declaration states that the "aptamer was encapsulated into PLGA microspheres merely to provide sustained delivery of the EYE-001 aptamer to the surface of the eye." Dr. Carrasquillo then goes on to state her belief that encapsulation was not necessary to facilitate the delivery of the nucleic acid through the sclera.

Furthermore, the specification describes various means for providing nucleic acids onto the scleral surface. For example, Applicants submit that the second full paragraph appearing on page 12 of the specification make clear that osmotic pumps, mechanical pumps and biodegradable polymers can release the agents of interest for delivering to the scleral surface. For example, Example 8 provides a protocol whereby a "undirectional osmotic pump may be used to deliver the FITC-IgG at a fixed rate to the orbital scleral surface of locally anesthetized rabbits" [page 28, lines 17-18, emphasis added]. Applicants submit that these approaches are used to provide a source of nucleic acid and are not required to facilitate transport of the nucleic acid across the sclera.

The Office Action also states that the poster (document C3) "indicates that the oligonucleotide-loaded microsphere is about 50 kDa. Thus the evidence submitted does not demonstrate that nucleic acids as large as 150 kDa can be delivered transclerally." Applicants wish to clarify that the oligonucleotide in the poster had a molecular weight of about 50 kDa, not the microsphere. However, Applicants submit that the skilled artisan, using the *in vitro* protocol described in Example 1, could determine whether, without any undue experimentation, nucleic acids of different sizes can traverse the scelera.

Also, the Office appears to be concerned that the specification does not disclose a particular nucleic acid that could be used in the claimed method. Applicants submit that the claimed delivery method has general applicability and need not be limited to a particular nucleic acid molecule. Applicants have made a valuable contribution to the art of ocular drug delivery

and to limit the invention to a particular nucleic acid sequence would render the claims essentially worthless. Applicants submit that the specification clearly discloses how to apply a nucleic acid to a scleral surface. This is all that is required by the claimed invention. In addition, Applicants have already provided evidence, for example in the poster of record as C3, the paper of record as C18, and the enclosed declaration from Dr. Carrasquillo, that show that the claimed delivery method is operable.

Applicants submit that the specification fully enables the skilled artisan to practice the full scope of the claimed invention. Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

***Rejection of Claims 1-18 and 21 Under***
***35 U.S.C. §112, First Paragraph***

According to pages 6-7 of the outstanding Office Action, claims 1-18 and 21 presently stand rejected under 35 U.S.C. §112, first paragraph, for containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor was in possession of the invention. Specifically, the Office states that the rejection "is based on lack of description of a **nucleic acid** molecule that could be used in practicing the method of the invention for 'diagnostic or therapeutic purposes.'" Applicants respectfully traverse this rejection to the extent that it is maintained over the pending claims for the following reasons.

Applicants submit that the claimed invention, for example, as recited in claim 1 is directed to a method of delivering a nucleic acid molecule into a mammalian eye. The method comprises contacting a scleral surface of the eye with a nucleic acid molecule having a molecular weight no greater than 150 kDa such that the nucleic acid passes through the sclera and into the interior of the eye. Applicants submit that the claimed delivery method is one of general applicability and, therefore, as noted previously should not be limited to any particular nucleic acid molecule.

At the outset, Applicants submit that the specification makes clear that they were in possession of the invention at the time the application was filed. Page 7, line 10 and page 9, lines

5-15 make clear that nucleic acids are one of the agents that can be delivered by the claimed invention.

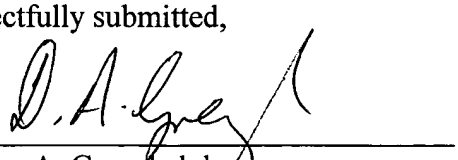
The Office appears to be taking the position that particular nucleic acids are essential to the claimed invention. Applicants disagree and submit that the claimed delivery method can be used for a variety of nucleic acid sequences. By way of example, Dr. Carrasquillo's declaration provides *in vivo* data showing that an anti-VEGF aptamer, which was available prior to the effective filing date of the application, can traverse the scelera and impart a biological effect within the interior of the eye. Furthermore, to the extent that claims relate to the delivery of nucleic acids useful in treating certain ocular disorders, Applicants submit that suitable nucleic acid sequences were available in the art and would have been known to the skilled artisan. For example, in the previous Amendment and Response, Applicants have already made of record a variety of documents that describe a variety of nucleic acids that had been delivered to the eye by other routes, for example, via intravitreal injection, prior to the filing date of this application. Applicants' invention provides another route to get such nucleic acids into the eye.

In view of the foregoing, Applicants submit that the specification provides ample written description of the claimed invention and, therefore, respectfully request that this rejection be reconsidered and withdrawn.

## ***CONCLUSION***

In view of the foregoing amendments and remarks, Applicants believe that the application is in condition for immediate allowance. Early favorable action is respectfully solicited.

Respectfully submitted,



Date: August 13, 2004
Reg. No. 38,678

Duncan A. Greenhalgh
Attorney for Applicant(s)
Testa, Hurwitz, & Thibeault, LLP
High Street Tower
125 High Street
Boston, Massachusetts 02110

Tel. No.: (617) 248-7317
Fax No.: (617) 248-7100